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Steroid refractory dermatomyositis following combination dabrafenib and trametinib therapy

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Sir, An 81 year old lady presented 9 weeks after starting dabrafenib 100mg BD and trametinib 2mg OD for metastatic melanoma, complaining of progressive proximal muscle weakness, associated with a violaceous macular rash in a V-shaped distribution on the anterior chest, myalgia, facial swelling, profound fatigue, and loss of appetite. She was diagnosed with stage III melanoma in 2013, and underwent local excision and lymph node resection at the time; however, she relapsed in 2016, developing new cutaneous lesions and lungs metastases. Otherwise she had no significant past medical history or regular medications. On examination, neck drop was noted, and proximal power was reduced to Medical Research Council (MRC) scale 3/5 in the upper limbs and 4/5 in the lower limbs. Dabrafenib and trametinib were discontinued, pending further investigations. MRI and CT imaging of the head and neck revealed no underlying cause and a paraneoplastic antibody screen was negative; however creatinine phosphokinase and CRP were elevated (1350 U/L and 22 mg/L respectively), and an EMG showed small, short duration polyphasic units, consistent with the clinical diagnosis of dermatomyositis (2017 EULAR/ACR classification criteria: definite idiopathic inflammatory myopathy; subgroup dermatomyositis; 99% probability). She had a borderline ANA of 1:100 but antibodies to Sm, RNP, SSA, SSB and Scl-70 were negative as were myositis specific autoantibodies to EJ, Jo-1, Ku, Mi-2, OJ, PL-12, PL-7, PM-Scl100, PM-Scl75 and SRP. There was no clinical response to 60mg prednisolone, and although there was a reduction in CK and CRP this was not sustained with 40mg prednisolone. Despite continued high dose steroids she went on to develop new periungual lesions, nail fold capillary changes, Gottron's sign over the metacarpophalangeal joints, and an unsafe swallow, requiring a PEG insertion. Two doses of IVIg (2g/kg) were administered 8 weeks apart, producing an excellent clinical response, with resolution of dysphagia, power 5/5 throughout, and normalisation of CRP. Sixteen weeks later she developed a mild recurrence of weakness and the macular rash. Further IVIg was administered and then continued at 8 weekly intervals. She remains off dabrafenib and trametinib and has declined further therapy for melanoma.

Dermatomyositis (DM) belongs to a heterogeneous group of autoinflammatory myopathies featuring symmetrical proximal muscle weakness, with or without systemic manifestations. It may occur as a paraneoplastic phenomenon, sometimes several months/years before a formal diagnosis of malignancy. Nevertheless, the temporal association between the onset of DM and treatment with dabrafenib/ trametinib in our case raises the possibility of a drug-associated trigger. Notably, interstitial lung disease, myalgia, arthralgia and synovitis, have all been reported as individual side effects of dabrafenib and trametinib, and CRP often increases with use of these treatments.

Dabrafenib and trametinib inhibit two kinases, BRAF and MEK1/2 respectively, within the mitogen-activated protein kinases/extracellular signal regulated kinases (MAPK/ERK) signalling pathway. They are used alone or in combination for melanoma. Overactivity of the MAPK/ERK pathway in BRAFv600 mutated melanoma cells drives tumour growth by promoting entry into the cell cycle. However activation of the MAPK/ERK pathway is also important for T cell receptor signalling and is critical for naive T cell activation with effects on other T cell subsets dependent upon context and state of differentiation.[1] Emerging evidence suggests that overactivity of the MAPK/ERK pathway in melanoma induces an immunosuppressive environment conducive to propagation of the tumour through mechanisms including downregulation of HLA class 1 expression by tumour cells and TGFβ-dependent induction of T regulatory (Tregs) cells.[2, 3] Experimental evidence suggests that MAPK/ERK pathway inhibition may increase the number and activity of CD8+ tumour infiltrating lymphocytes, and also more generally reduce Treg function which might impair peripheral tolerance.[4, 5] Consequently there is the potential for therapeutic synergy between MAPK/ERK pathway inhibitors and tumour immunity promoting checkpoint blockade.[1]

Malignancy-associated dermatomyositis may be driven by an immune response to autoantigens on tumour cells that crossreact with the same antigens being expressed on regenerating muscle fibres.[6] Treg depletion exacerbates disease in animal models,[7] and increased numbers of Tregs in muscle were observed following abatacept treatment of refractory inflammatory myositis.[8]

Therefore it seems plausible that MAPK/ERK pathway inhibition may both enhance tumour immunity and also facilitate priming of an autoimmune muscle response, further aggravated by possible suppression of Treg function.

Immune-related adverse events following checkpoint blockade for melanoma and other cancers are becoming increasing well-recognised amongst rheumatologists. However the potential for such events to follow combination Dabrafenib and Trametinib is not well appreciated. We have reported a case of steroid-refractory dermatomyositis with temporal association to Dabrafenib and Trametinib therapy. Physicians should be aware of the possibility of autoimmune sequelae arising with these drugs.

Key Message

Autoimmune events may arise following therapy with MAPK/ERK pathway inhibitors

Conflict of Interest

BAF has received consultancy fees from Novartis, Roche, MedImmune and BMS.

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References

1. Ebert PJR, Cheung J, Yang Y, McNamara E, Hong R, Moskalenko M, Gould SE, Maecker H, Irving BA, Kim JM *et al*: **MAP Kinase Inhibition Promotes T Cell and Anti-tumor Activity in Combination with PD-L1 Checkpoint Blockade**. *Immunity* 2016, **44**(3):609-621.
2. Hossain DM, Panda AK, Chakrabarty S, Bhattacharjee P, Kajal K, Mohanty S, Sarkar I, Sarkar DK, Kar SK, Sa G: **MEK inhibition prevents tumour-shed transforming growth factor-beta-induced T-regulatory cell augmentation in tumour milieu**. *Immunology* 2015, **144**(4):561-573.
3. Mandala M, De Logu F, Merelli B, Nassini R, Massi D: **Immunomodulating property of MAPK inhibitors: from translational knowledge to clinical implementation**. *Laboratory investigation; a journal of technical methods and pathology* 2017, **97**(2):166-175.
4. Kalland ME, Oberprieler NG, Vang T, Tasken K, Torgersen KM: **T cell-signaling network analysis reveals distinct differences between CD28 and CD2 costimulation responses in**

various subsets and in the MAPK pathway between resting and activated regulatory T cells. *Journal of immunology (Baltimore, Md : 1950)* 2011, **187**(10):5233-5245.
5. Lieske NV, Tonby K, Kvale D, Dyrhol-Riise AM, Tasken K: **Targeting Tuberculosis and HIV Infection-Specific Regulatory T Cells with MEK/ERK Signaling Pathway Inhibitors**. *PLoS One* 2015, **10**(11):e0141903.
6. Casciola-Rosen L, Nagaraju K, Plotz P, Wang K, Levine S, Gabrielson E, Corse A, Rosen A: **Enhanced autoantigen expression in regenerating muscle cells in idiopathic inflammatory myopathy**. *The Journal of experimental medicine* 2005, **201**(4):591-601.
7. Allenbach Y, Solly S, Gregoire S, Dubourg O, Salomon B, Butler-Browne G, Musset L, Herson S, Klatzmann D, Benveniste O: **Role of regulatory T cells in a new mouse model of experimental autoimmune myositis**. *The American journal of pathology* 2009, **174**(3):989-998.
8. Tjarnlund A, Tang Q, Wick C, Dastmalchi M, Mann H, Tomasova Studynkova J, Chura R, Gullick NJ, Salerno R, Ronnelid J *et al*: **Abatacept in the treatment of adult dermatomyositis and polymyositis: a randomised, phase IIb treatment delayed-start trial**. *Ann Rheum Dis* 2018, **77**(1):55-62.